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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/987,482	11/14/2001	Pooman Bhandari	056859-0134	7065

22428 7590 10/08/2004

FOLEY AND LARDNER
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EXAMINER	
PRIEBE, SCOTT DAVID	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 10/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/987,482	BHANDARI ET AL.	
	Examiner	Art Unit	
	Scott D. Priebe	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The Group and/or Art Unit designation of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Primary Examiner Scott D. Priebe, Ph.D., Group Art Unit 1632.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/9/04 has been entered.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Objections

Claims 38-41 and 43-46 are objected to because of the following informalities. In claim 38, line 3 of part (b), "abnormality" should be plural. In claims 38 and 42, semi-colons, not commas, should be used for separating members of a list flowing a colon. In claims 39-41 and 43-46, the first word "A" should be --The--, since these are dependent claims. In claim 40, "comprise promoter" should be --comprise promoters-- ; however, see new matter rejection under 35 USC 112, 1st para. In claim 41, "adult epidermal development" does not make sense as a selected "abnormality". Also in claim 41, "tergites that and are devoid" is grammatically

incorrect. In claim 42, line 3, "files" should be --flies--. In claim 43, "anti-inflammatory" is used as a noun, but it is an adjective. In claim 46, line 3, "and" should be deleted, and the period following "pigmentation" (line 3) should be deleted. Appropriate correction is required.

Claim Rejections - 35 USC § 112

Claims 38-46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. New claims 38-46 contain new matter that is not fully supported by the original application.

Claims 38-46 are new claims, which differ substantially from the cancelled claims previously examined. Applicant has not indicated where or how the subject matter of these claims are supported by the original application, as is Applicant's burden. See MPEP 714.02, last sentence of the third paragraph from the end and 2163.06 (I) last sentence.

Claims 38-41 are directed to a transgenic *Drosophila* made by inserting a DNA encoding human APC protein of SEQ ID NO: 1 (hAPC/FL) into a generic P-element vector and introducing the vector into an embryo of *Drosophila* strain *w; Δ2-3Ki*, such that the hAPC protein leads to one or more developmental abnormalities of the embryo. A fly arising form the embryo is then crossed with another transgenic *Drosophila* having "*GAL4* promoters," and the resulting transgenic fly expresses SEQ ID NO: 1.

First, the only mention in the specification of P-element vectors in the context of the claimed subject matter is in Example 1, referring specifically to pCaSpeR-UAS and *w; Δ2-3Ki* embryos. There is no mention, even in passing, of using a generic P-element vector to make transgenic flies in general, or with *w; Δ2-3Ki* embryos specifically. Consequently, the claims are broader in scope than the original description. Claim 38 should be amended to recite that the DNA is inserted into the P-element vector pCaSpeR-UAS (and claim 39 cancelled). Taking characteristics of an individual embodiment and making that characteristic the basis of a generic claim without further supporting disclosure is not in compliance with the written description requirement. See *Purdue Pharma L.P. v. Faulding Inc.*, 56 USPQ2d 1481, 1487 (CAFC 2000).

Second, there is no mention in the specification that the initial transgenic embryo or fly made by step (b) displays any phenotype, much less any developmental abnormalities. Third, there is no mention of crossing the initial transgenic fly into a transgenic line of "fly having *GAL4* promoters." Although not stated in the specification, it appears that the hAPC coding DNA is under control of a *GAL4* UAS. The reason one crosses the initial transgenic fly into a GAL4 driver line (not a "fly having *GAL4* promoters") is so that the transgene in the P-element, which is presumed by the Examiner to be under transcriptional control of a *GAL4* UAS (promoter), will be expressed specifically in the cells expressing the GAL4 protein. A GAL4 driver line is a line of transgenic *Drosophila* comprising a coding sequence for GAL4 protein in operable linkage to a promoter of interest, usually an endogenous promoter. The identity of the cells in the fly expressing GAL4 depends upon the specific promoter to which the GAL4 coding sequence is linked, and thus on the specific GAL4 driver line. See specification, page 11, lines 8-14.

Claim 40 is directed to embodiments wherein the claimed fly "comprise promoters from *vg*-GAL4, *ptc*-GAL4, and *ey*-GAL4" (*sic*). The original specification does not support or describe such embodiments. First, *vg*-GAL4, *ptc*-GAL4, and *ey*-GAL4 each refer to specific GAL4 driver lines, not "promoters." Second, there is no suggestion in the specification of crossing the initial transgenic fly into a driver line that contains all three of the *vg*-GAL4, *ptc*-GAL4, and *ey*-GAL4 transgenes. Finally, the specification does not describe crossing a transgenic fly comprising a hAPC/FL transgene into a *vg*-GAL4 driver line. Rather, it describes crossing a fly specifically with the hAPC/CBD transgene into this driver line. There is no general teaching for crossing into the *vg*-GAL4 driver line. One cannot use details from a specific embodiment as the basis for a generic claim, *Purdue Pharma.*

Claim 41 is directed to embodiments where the transgenic fly has an abnormality of "adult epidermal development, incomplete development of dorsal tergites that and are devoid of pigmentation." Only one species embraced by the claims is disclosed with an abnormality in epidermal development. Step (c) was carried out with the *ptc*-GAL4 driver line, and the only observed abnormality in adult epidermis was dorsal tergites that were not properly developed and were devoid of pigmentation (page 18, lines 6-10). Ectopic expression of Dpp and leg duplications, specifically of claws and sex combs, were also reported only with the cross into the *ptc*-GAL4 driver line (page 18). There appears to be no mention of a transgenic fly with loss of wing. With respect to inappropriate patterning of ommatidia (page 18, lines 24-29), this is describing overexpression of Dpp or loss of Wg, not mis-expression of hAPC. Mis-expression of hAPC in flies, specifically from an *ey*-GAL4 driver cross, resulted specifically in ectopic ommatidia (page 19, lines 1-6).

Claims 42-46 are directed to a method of using generic transgenic *Drosophila* flies expressing hAPC (SEQ ID NO: 1) for screening and validating efficacy of pharmaceutical drugs. Claim 43 recites that such drugs include analgesics, antipyretics, anti-inflammatory (*sic*) and antineoplastics. However, the specification repeatedly discloses that the transgenic flies mis-express hAPC/FL "in a regulated manner" (e.g. page 8). The only "regulated manner" described is by crossing a transgenic fly made as in Example 1 into GAL4 driver lines. Thus, with respect to the scope of the transgenic fly, the claimed subject matter is broader than originally described. With respect to particular types of drugs to be screened, the specification teaches (page 12, line 24 to page 13, line 7, and page 14, lines 8-18) that it is specifically anti-cancer drugs that are being screened and validated, specifically by looking for those that enhance developmental abnormalities induced by mis-expression of hAPC/FL in a regulated manner. The specification (page 14, lines 21-23) briefly mentions using analgesics, antipyretics, anti-inflammatory (*sic*) and antineoplastics in an embodiment wherein "human APC pathway is identified." It is unclear what this means, but it is apparent that it does not mean "screening and validating efficacy" of the drugs.

Claim 44 recites a dose range for the drug concentration. However, the specification specifically discloses that this concentration range is in fly food (e.g. page 11. lines 29-30; page 14, lines 25-26). The scope of the claim is broader than that originally described.

Claims 39 and 40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described

in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The application discloses the P-element vector pCaSpeR-UAS and transgenic *Drosophila* GAL4 driver lines *vg*-GAL4, *ptc*-GAL4, and *ey*-GAL4, that are encompassed by the definitions for biological material set forth in 37 C.F.R. § 1.801. Because it is apparent that this biological material is essential for practicing the invention as claimed, it must be obtainable by a reproducible method set forth in the specification or otherwise be known and readily available to the public as detailed in 37 C.F.R. §§ 1.801 through 1.809.

The specification does not provide any instruction as to the structure of pCaSpeR-UAS. The specification does not describe how *vg*-GAL4, *ptc*-GAL4, and *ey*-GAL4 lines are made. It is unclear whether this biological material is known and readily available to the public. The specification refers to Brand and Perrimon (1993) as the source of the plasmid (Example 1) and *ptc*-GAL4 line (Example 3). However, this reference makes no mention of pCaSpeR-UAS, much less describe what the plasmid is or how to make or obtain it; nor does it mention *ptc*-GAL4. Hazelett is cited as disclosing *ey*-GAL4 (Example 3). While it mentions using this line, it does not describe what it is or how it was made. Simmonds is cited as disclosing *vg*-Gal4 (Example 3). While Simmonds mentions *vg*-GAL4, it does not describe what it is or how it was made (it states that it was obtained from someone else, legend of Fig. 3). Accordingly, availability of such biological material is deemed necessary to satisfy the enablement provisions of 35 U.S.C. § 112. If this biological material is not obtainable or available, the requirements of 35 U.S.C. § 112 may be satisfied by a deposit of the biological material. In order for a deposit to meet all criteria set forth in 37 C.F.R. §§ 1.801-1.809, applicants or assignee must provide assurance of compliance

with provisions of 37 C.F.R. §§ 1.801-1.809, in the form of a declaration or applicant's representative must provide a statement. The content of such a declaration or statement is suggested by the enclosed attachment. Because such deposit will not have been made prior to the effective filing date of the instant application, applicant is required to submit a verified statement from a person in a position to corroborate the fact, which states that the biological material which has been deposited is the biological material specifically identified in the application as filed (37 C.F.R. § 1.804). Such a statement need not be verified if the person is an agent or attorney registered to practice before the Office. Applicant is also reminded that the specification must contain reference to the deposit, including deposit (accession) number, date of deposit, name and address of the depository, and the complete taxonomic description.

Claims 42-46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using the method for screening drugs for their effect on the phenotype of the flies, does not reasonably provide enablement for "validating efficacy" of the drugs. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are directed to a method "for screening and validating efficacy of pharmaceutical drugs." The specification does not explain exactly what "validating efficacy" means in this context, but is presumed to mean confirming that the drug is efficacious for use as a pharmaceutical. The specification does not explain how the method can be used to "validate" efficacy of a pharmaceutical drug.

The only such use described in the specification in this context is treating colon cancer. The only types of drug that are clearly taught for use in this method are anti-cancer drugs. See page 27. Four known anti-colon cancer drugs, 5-fluoruracil, pyroxicam, aspirin and indomethacin, were tested for their effects on the eye phenotypes of developing transgenic flies expressing hAPC in an *ey*-GAL4 driver background. The last three are non-steroidal anti-inflammatory drugs (NSAID). Treatment of wild type flies had no obvious phenotype, and treatment of the transgenic flies with any of the first three anti-colon cancer drugs resulted in no significant phenotypic changes. Only indomethacin treatment induced an obvious change, making the eye phenotype of the transgenic flies more severe, sometimes to the loss of eyes, i.e. enhanced the effect of hAPC mis-expression. This result suggests that indomethacin may affect a component of a pathway that includes APC. He (1999) discloses that the basis for the anti-colon cancer activity of NSAIDs is unlikely to be mediated through COX receptors, so it is unlikely that the claimed assay would be useful for validating the efficacy of NSAIDs as anti-inflammatory drugs. He suggests that the anti-colon cancer activity may be mediated by decreasing PPARδ activity, similar to the effect of APC which represses PPARδ expression (and thus decreases its activity).

While the method may be useful for elucidating the mechanism by which particular anti-colon cancer drugs, e.g. indomethacin, act or identify other possible targets for anti-colon cancer drugs (spec. page 28), the lack of an effect seen with 5-flurouracil and especially the other two NSAIDs, pyroxicam and aspirin, raises doubt as to how the method would be used for "validating efficacy" of drugs in general, or anti-colon cancer drugs in particular. As mentioned above, He discounts the anti-cancer activity of NSAIDs is related to their anti-inflammatory and

pain relieving activity on COX receptors. It is perhaps not surprising that 5-flurouracil had no effect on the fly's phenotype, since its mode of action in treating colon cancer is expected to be quite different than that of the NSAIDs. However, the results of the disclosed working example could be said to invalidate, rather than validate, the efficacy of the other two anti-colon cancer drugs, aspirin and pyroxicam. With these conflicting results, it is then unclear how the method validates the efficacy of indomethacin. The performance of a particular anti-cancer drug in the claimed assay appears to be unrelated to its performance in treating colon cancer.

It is suggested that the preamble be amended to more accurately describe the use(s) of the method, such as screening for compounds that affect the APC pathway or for elucidating mechanism of action of anti-colon cancer drugs.

Claims 42-46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 42 recites the limitation "the phenotypic changes" in the last line. Claim 45 recites "the compound." There is insufficient antecedent basis for these limitations in the claims.

Claim 42 (and its dependent claims) is incomplete. The recited method steps do not clearly relate back to the preamble of the claim. The claim does not indicate how step (c) results in validating efficacy of the drugs.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe whose telephone number is (571) 272-0733. The examiner can normally be reached on M-F, 8:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy J. Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Scott D. Priebe

Scott D. Priebe
Primary Examiner
Art Unit 1632

SUGGESTION FOR DEPOSIT OF BIOLOGICAL MATERIAL ATTACHMENT

A declaration by applicant or assignee, or a statement by applicant's agent identifying a deposit of biological material and averring the following may be sufficient to overcome an objection or rejection based on a lack of availability of biological material. Such a declaration:

1. Identifies declarant.

2. States that a deposit of the material has been made in a depository affording permanence of the deposit and ready accessibility thereto by the public if a patent is granted. The depository is to be identified by name and address. (See 37 C.F.R. § 1.803).

3. States that the deposited material has been accorded a specific (recited) accession number.

4. States that all restrictions on the availability to the public of the material so deposited will be irrevocably removed upon the granting of the patent. (See 37 C.F.R. § 1.808(a)(2)).

5. States that the material has been deposited under conditions that assure that access to the material will be available during the pendency of the patent application to one determined by the Commissioner to be entitled thereto under 37 C.F.R. § 1.14 and 35 U.S.C. § 122. (See 37 C.F.R. § 1.808(a)(1)).

6. States that the deposited material will be maintained with all the care necessary to keep it viable and uncontaminated for a period of at least five years after the most recent request for the furnishing of a sample of the deposited microorganism, and in any case, for a period of at least thirty (30) years after the date of deposit or for the enforceable life of the patent, whichever period is longer. See 37 C.F.R. § 1.806).

7. That he/she declares further that all statements made therein of his/her own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the instant patent application or any patent issuing thereon.

Alternatively, it may be averred that deposited material has been accepted for deposit under the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure (e.g., see 961 OG 21, 1977) and that all restrictions on the availability to the public of the material so deposited will be irrevocably removed upon the granting of a patent.

Additionally, the deposit must be referred to in the body of the specification and be identified by deposit (accession) number, date of deposit, name and address of the depository, and the complete taxonomic description.